EXHIBIT J

Prospective study of depression and anxiety in female fertility preservation and infertility patients

Angela K. Lawson, Ph.D.,[a] Susan C. Klock, Ph.D.,[a] Mary Ellen Pavone, M.D.,[a] Jennifer Hirshfeld-Cytron, M.D.,[b] Kristin N. Smith, B.S.,[a] and Ralph R. Kazer, M.D.[a]

[a] Northwestern University, Chicago; and [b] Fertility Centers of Illinois, Orland Park, Illinois

Objective: To prospectively assess anxiety, depression, coping, and appraisal in female fertility preservation (FP) patients compared with infertile patients.
Design: Prospective pre- and post-treatment survey.
Setting: Academic medical center.
Patient(s): Forty-seven women with cancer (FP patients) and 91 age-matched infertile patients.
Intervention(s): None.
Main Outcome Measure(s): Depression, anxiety, coping, infertility-related stress, appraisal of treatment, and medical outcomes.
Result(s): FP patients reported more symptoms of anxiety and depression than infertile patients, but infertile patients' symptoms worsened over time; 44% of FP and 14% of infertile patients' scores exceeded the clinical cutoff for depression before treatment. The interval between surveys and medical treatment data did not predict changes in mood symptoms. Coping strategies and infertility-related stress did not differ between groups, and avoidant coping predicted higher depression and anxiety scores.
Conclusion(s): FP patients reported more anxiety and depression than infertile patients at enrollment in treatment, with more than one-third of FP patients reporting clinically significant depressive symptoms. However, infertile patients' anxiety and depressive symptoms increased across treatment. This increase was not related to time between registration for IVF and oocyte retrieval or the medical aspects of treatment. FP and infertile patients should be provided psychologic consultation before treatment to identify mood and anxiety symptoms and to refer patients for counseling as needed to prevent worsening of symptoms. (Fertil Steril® 2014;102: 1377–84. ©2014 by American Society for Reproductive Medicine.)
Key Words: Fertility preservation, IVF, psychologic, counseling

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Young cancer patients are increasingly interested in preserving their fertility before undergoing gonadotoxic therapies (1–5). Female cancer patients can preserve their fertility by undergoing embryo or oocyte cryopreservation before beginning cancer treatment (6). Oocytes or embryos can be cryopreserved and stored until the cancer has been treated and the woman is ready to attempt pregnancy. Although the medical safety and treatment protocols for fertility preservation (FP) via controlled ovarian hyperstimulation (COH) have been well documented (1–4, 7), there is limited research addressing the psychologic issues that arise in FP patients. Based on the research describing the emotional aspects of in vitro fertilization (IVF) for infertile couples (8), the psychosocial stressors associated with IVF or FP likely include the physical and emotional side effects of medications and procedures (9–12), treatment expense (13–17), relationship changes after embryo cryopreservation which may interfere with a patient's use of the embryos (18–21), and religious/ethical issues related to embryo disposition (14, 22–25).

IVF, though providing the hope of family building opportunities, has also been perceived by patients to be a stressful experience (26). Coping with IVF can be conceptualized from the stress and coping model of Lazarus

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Reprint requests: Angela K. Lawson, Ph.D., Department of Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine, 676 North St. Clair Street, Suite 1845, Chicago, Illinois 60611 (E-mail: alawson@nmff.org).

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and Folkman (27). This model has been used in earlier studies of the stress of infertility but has not been applied to studies of the psychological adjustment to FP (28–30). In this model, psychologic harm is mediated by an individual's appraisal of the event and the ways in which they cope with the event. If the individual appraises the event as harmful or threatening, and their stress overwhelms their coping resources or results in problematic coping, such as ignoring the problem, then depression and/or anxiety may result.

Research on infertile IVF patients has found that 20%–50% report mild to moderate symptoms of depression, 2% report severe symptoms of depression, 15%–56% report clinically significant anxiety, and these symptoms worsen after failed treatment cycles (31–33). Of the few studies that have been conducted with FP patients, it has been found that a considerable percentage of FP patients also experience emotional distress during treatment with as many as one-third reporting significant anxiety or depression symptoms and 14% taking prescribed antidepressant medication (5, 14). These rates of anxiety and depression are similar to those reported by Peate et al., in which 32% of young breast cancer patients reported symptoms of anxiety and 10% reported symptoms of depression (34).

In addition to the similarities across infertile and FP patients' experiences, there are unique stressors for both groups. Specifically, infertile patients are concerned about immediate chances of pregnancy, whereas FP patients are in the early stages of coping with their cancer diagnosis. FP patients have cancer-specific concerns about their mortality, future disease recurrence, implications of genetic testing (e.g., *BRCA*), body image concerns, and are concerned about the effects of cancer treatment on their sexuality as well as on current and future relationships (14, 16, 35–39). FP patients are also likely to have fertility treatment–specific concerns about the health consequences of delaying their cancer treatment to pursue FP, the potential effect of high doses of injectable gonadotropins on cancer recurrence (especially with hormonally sensitive cancer types), the need to make treatment decisions within days or weeks (17, 24, 35, 40), and the emotional consequences of posthumous reproduction should they ultimately succumb to their disease (7, 41–43).

The multiple differences in the emotional aspects of IVF for infertile patients and FP treatment via COH may result in differences in the psychologic experiences of these two groups during treatment. However, there have been no prospective assessments of the psychologic status of FP patients as they undergo treatment and no direct comparison of the psychologic experiences of FP and infertile patients. The purpose of the present study was to describe the occurrence of symptoms of depression and anxiety in FP and infertility patients at the onset of COH treatment and examine the change in depression and anxiety symptoms across each patient's first treatment cycle. In addition, we hypothesized that negative appraisals of treatment and problematic coping (i.e., avoidance and internet use) are related to higher scores on measures of depression and anxiety.

MATERIALS AND METHODS

Participants

The sample included 47 consecutive premenopausal female FP patients and 91 consecutive prospectively age-matched female infertile patients who were beginning their first cycle of COH from 2011 to 2013. Two additional FP patients were not included in the study because they consented to participate in the study but did not complete either questionnaire. Four FP and 4 infertile patients declined study enrollment. Patients who were <18 years old or were non–English speaking were excluded from the study.

Procedures

All participants had a routine pretreatment registration appointment that included physician, nurse, and psychologist consultations. The study participants completed two questionnaires. The pretreatment survey (T1; 175 items) was administered at the time of registration for COH treatment and the post-COH survey was completed before sedation on the day of oocyte aspiration (T2; 104 items). The post-COH survey was administered at that time to assess the subject's emotional state after exposure to ovarian stimulation but before pregnancy. Thus we could assess the relationship of a measure of mood unaffected by knowledge of pregnancy outcomes with later assessments of dependent variables. The surveys contained questions about the patients' demographics and medical history, including age, marital status, reproductive history, racial/ethnic status, mental health history, insurance coverage, and previous cancer treatment. Treatment data included gonadotropin dosage, antimüllerian hormone (AMH) values, peak E_2, oocyte quality and quantity, pregnancy data, and treatment expectations.

Measures

1. Depressive symptomatology was assessed at both time points with the use of the Center for Epidemiologic Studies Depression Scale (CES-D; a 20 item, Likert scaled questionnaire) (44), with higher scores reflecting greater symptomatology. Scale scores of 16–21 indicate mild–moderate depressive symptomatology, and scores >21 indicate probable major depression.
2. The State-Trait Anxiety Inventory (STAI) (45) was used to assess both current (STAI-S; state) and general (STAI-T; trait) levels of anxiety. The STAI contains 40 Likert-scale items, with higher scores reflecting greater symptomatology and a suggested cutoff of 39 for clinically significant anxiety (46). State anxiety was measured at both time points, and trait anxiety was measured only at T1.
3. The Ways of Coping–Revised scale (WOC-R) contains 29 Likert-scale items and was used at both time points to measure three dimensions of coping: self-blame and avoidance [SBA], informational and emotional support seeking [IES], and cognitive restructuring [CR]). Higher scores on the WOC-R subscales reflect more coping activity (47).
4. Appraisal of Life Events scale (ALE) (48) was used at both time points to assess three dimensions of the cognitive

appraisal of treatment: threat, challenge, and loss. The ALE has 16 Likert-scale items, with higher scores indicating greater appraisal.

5. Fertility Problems Inventory (FPI) (49), a 46-item measure, was used at T1 to assess five dimensions of infertility-related stress: social concern, sexual concern, relationship concern, rejection of childfree lifestyle, and need for parenthood.

After completion of the treatment cycle, the subjects' IVF medical data were obtained via chart review. Treatment data included gonadotropin dosage, AMH values, peak E_2, oocyte quality and quantity, embryo quality and quantity, pregnancy data, and treatment expectations. The study was approved by the Institutional Review Board at Northwestern University.

Statistical Analysis

Statistical analyses were performed with the use of SPSS (IBM) using parametric tests for normally distributed data and nonparametric tests for nonnormally distributed data, unequal sample variances, categoric data, and/or comparisons with small sample sizes. Logistic multiple regression analyses were used to test the model for appraisal and coping as predictors of depression and anxiety. Analyses were based on available data, sample sizes are provided, and $P<.05$ (2 tailed) was considered to be significant.

RESULTS

The average age of women undergoing FP was 31.84 years old (range 19–39, SD 2.39) and the average age of the age-matched infertile comparison group was 31.49 (range 26–36, SD 4.76), a nonsignificant difference. The majority of women in both groups were white, were nulligravid, and had completed at least a college degree. Although the majority of women in both groups had a spouse or heterosexual partner, fewer of the FP women (46.8%) were married compared with the women in the infertile comparison group (95.6%; $P<.001$). Furthermore, despite treatment occurring in a state with an insurance mandate for fertility treatment coverage, only 23.4% of FP patients had most of their treatment expenses covered by their insurance, compared with 56% of those in the infertile comparison group ($P<.001$). The demographic characteristics of the two groups are presented in Table 1.

The majority of FP patients had been diagnosed with breast cancer (63.8%), and 12.8% of patients had been diagnosed with a hematologic cancer (i.e., leukemia or lymphoma), 12.8% with a gynecologic cancer, and 10.6% with brain or colon cancer. Three FP patients (two with a hematologic cancer and one with brain cancer) presented with a history of previous chemotherapy treatment. The median time interval between registration for treatment and oocyte retrieval was significantly shorter ($P<.05$) for FP patients (14.0 days, range 10–62) than for the infertile comparison group (38.5 days, range 11–200).

Median scores and significant group differences for the FP patients and the infertile comparison group on all psychologic measures are listed in Table 2. Overall, FP patients reported more symptoms of depression and anxiety than infertile control subjects. Group differences were also found in measures of appraisal and coping but not specific fertility-problem stress. Forty-four percent (17/39) of FP women, compared with 14% (10/74) of the infertile comparison group, had a score >16 on the CES-D at T1. Sixty-two percent of FP women, compared with 27% of the infertile comparison group, had STAI-S scores ≥39 at T1. At the time of the pretreatment psychologic consultation, in terms of self-reported anxiety and depression disorders, 13% (6/46) of FP patients reported a current depressive disorder and

TABLE 1

Demographic characteristics of (n = 47) fertility preservation and (n = 91) infertile control participants who began a cycle of COH, n (%).

Variable	Fertility preservation	Infertile control
Ethnicity		
White	36 (76.6)	68 (74.7)
African American	1 (2.1)	2 (2.2)
Asian	3 (6.4)	11 (12.1)
Hispanic	5 (10.7)	4 (4.4)
Other	2 (4.3)	1 (1.1)
Unknown	0 (0)	5 (5.5)
Marital Status[a]		
Single	13 (27.7)	0 (0)
Married	22 (46.8)	87 (95.6)
Partnered	11 (23.4)	2 (2.2)
Unknown	1 (2.1)	2 (2.2)
Gravidity		
Never pregnant	32 (68.1)	65 (71.4)
1 pregnancy	11 (23.4)	15 (16.5)
≥2 pregnancies	4 (8.6)	8 (8.8)
Unknown	0 (0)	3 (3.3)
Parity		
No children	38 (80.9)	79 (86.8)
1 child	7 (14.9)	7 (7.7)
≥2 children	2 (4.3)	2 (2.2)
Unknown	0 (0)	3 (3.3)
Elective abortion		
None	40 (85.1)	80 (87.9)
1	7 (14.9)	4 (4.4)
≥2	0 (0)	1 (1.1)
Unknown	0 (0)	6 (6.6)
Miscarriage		
None	44 (93.6)	73 (80.2)
1	3 (6.4)	9 (9.9)
≥2	0 (0)	2 (2.2)
Unknown		7 (7.7)
Education		
High school diploma	1 (2.1)	1 (1.1)
Some college	4 (8.5)	0 (0.0)
College graduate	19 (40.4)	33 (36.3)
Some graduate school	2 (4.3)	6 (6.6)
Graduate school degree	18 (38.3)	45 (49.5)
Unknown	3 (6.4)	6 (6.6)
Insurance coverage for IVF[a]		
Most expenses covered	11 (23.4)	51 (56.0)
50% of expenses covered	3 (6.4)	13 (14.3)
<50% expenses covered	0 (0)	2 (2.2)
No coverage	19 (40.4)	7 (7.7)
Unknown	14 (29.8)	18 (19.8)

[a] $P<.001$.

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TABLE 2

Psychologic characteristics of fertility preservation and infertile control participants who began a cycle of controlled ovarian hyperstimulation, median (range).

Variable	Fertility preservation	Infertile control
CES-D T1[a,c]	13.0 (1–41)	6.0 (0–29)
CES-D T2	11.0 (1–37)	9.0 (0–41)
STAI-State T1[a,c]	41.0 (20–74)	32.5 (20–66)
STAI-State T2	38.5 (20–64)	40.0 (22–62)
STAI-Trait T1[a]	35.0 (24–59)	31.0 (23–62)
ALE T1		
Loss[c]	3.0 (0–10)	4.0 (0–15)
Threat	5.5 (0–19)	5.0 (0–24)
Challenge[a]	9.0 (1–24)	12.0 (1–28)
ALE T2		
Loss[b]	2.0 (0–16)	3.0 (0–12)
Threat	3.5 (0–20)	5.0 (0–19)
Challenge	8.0 (3–22)	10.0 (2–25)
FPI T1		
Social concern	22.0 (10–54)	26.0 (10–43)
Sexual concern	14.0 (8–33)	16.0 (8–36)
Relationship concern	16.0 (10–35)	17.0 (10–39)
Reject child-free lifestyle	25.0 (9–36)	29.0 (14–42)
Need for parenthood	38.5 (12–48)	38.5 (11–54)
WOC T1		
Self-blame/avoidance	12.0 (0–30)	10.0 (0–31)
Support seeking[d]	11.0 (4–19)	11.0 (1–20)
Cognitive restructuring	7.0 (2–13)	6.0 (0–14)
WOC T2		
Self-blame/avoidance	10.0 (2–32)	12.0 (1–29)
Support seeking[d]	9.0 (2–17)	10.0 (2–19)
Cognitive restructuring	7.0 (0–15)	6.0 (1–15)

[a] $P<.05$ (at time 1; Mann-Whitney U test).
[b] $P<.05$ (at time 2; Mann-Whitney U test).
[c] $P<.05$ (change from T1 to T2 in infertile control subjects; Wilcoxon signed ranks test).
[d] $P<.05$ (change from T1 to T2 in fertility preservation patients; Wilcoxon signed ranks test).

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TABLE 3

Correlation coefficients for variables significantly related to the CES-D or STAI-S.

Variable	CES-D T1	STAI-S T1	CES-D T2	STAI-S T2
CES-D T1	—			
STAIS-S T1	0.80[b]	—		
CES-D T2	0.70[b]	0.55[b]	—	
STAI-S T2	0.48[b]	0.40[b]	0.58[b]	—
ALE-Threat T1	0.30[b]	0.32[b]	0.30[b]	0.41[b]
ALE-Loss T1	0.33[b]	0.32[b]	0.43[b]	0.48[b]
WOC-SBA T1	0.69[b]	0.61[b]	0.51[b]	0.37[b]
WOC-IES T1	0.19	0.20[a]	0.05	0.13
FPI-SOCON T1	0.40[b]	0.36[b]	0.47[b]	0.27[a]
FPI-SEXCON T1	0.33[b]	0.37[b]	0.33[b]	0.28[a]
FPI-RCON T1	0.27[b]	0.21[a]	0.32[b]	0.04
ALE-Threat T2	0.18	0.12	0.36[b]	0.59[b]
ALE-Loss T2	0.20	0.17	0.38[b]	0.43[b]
WOC-SBA T2	0.47[b]	0.44[b]	0.59[b]	0.51[b]
AMH	−0.25[a]	−0.17	−0.07	0.05
Insurance	−0.31[b]	−0.29[a]	−0.16	−0.03

Note: T1 = time 1 survey; T2 = time 2 survey; CES-D = Center for Epidemiologic Studies Depression scale; STAI-S = State-Trait Anxiety Inventory State scale; ALE = Appraisal of Life Events scale; WOC = Ways of Coping–Revised scale; SBA = self-blame and avoidance; IES = informational and emotional support seeking; FPI = Fertility Problem Inventory; SOCON = social concern subscale; SEXCON = sexual concern subscale; RCON = relationship concern subscale; Insurance = coverage for treatment.
[a] $P<.05$ (two tailed).
[b] $P<.01$ (two-tailed).

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13% (6/46) reported a current anxiety disorder. Of the infertile comparison group, 9% (8/87) reported a current depressive disorder and 14% (12/87) a current anxiety disorder.

At T2, 32% (9/28) of FP patients had a score >16 on the CES-D at T2, compared with 23% (15/66) of the infertile comparison group; 50% of FP patients and 51% of the infertile comparison group had STAI-S scores >39 at T2. Scores on the CES-D and STAI-S were unchanged for FP patients and increased across survey periods for the infertile comparison group. Almost one-half (47%) of FP patients and only 18% of the infertile comparison group reported unrealistic treatment expectations, indicating that they believed that they had a greater than a 60% chance of pregnancy with each embryo transfer in IVF ($P<.05$). National data from the Society for Assisted Reproductive Technology indicates a pregnancy rate of ~50% for women <35 years old (50).

We were interested in examining the relationship between the role of coping and cognitive appraisal in the prediction of depression and anxiety. First, Spearman correlations between the psychologic measures, demographics, and medical variables were determined (Table 3). Only those variables with significant correlation coefficients were included in subsequent regression analyses (Table 3). We conducted hierarchic logistic regression to examine the ability of our measures to predict scores ≥16 on the CES-D and ≥39 on the STAI-S. Significant individual variables were entered into the first block. ALE threat and loss scores and FPI subscales were entered into the second block as both ALE and FPI measure perceived stress. The FPI was measured only at T1 but was included in models predicting T2 depression and anxiety because it was hypothesized to predict anxiety and depression at both time points. The relevant WOC subscales were entered into the final block because individuals do not engage in coping strategies unless they perceive an event as distressing. Group (i.e., FP or infertile comparison group) was excluded from the model because it was expected to account for major variance in depression or anxiety scores and would mask the importance of other predictors. A summary of regression results is listed below. Complete regression results may be obtained from the first author.

At T1, evaluation of the log-likelihood test of the overall model for depression (CES-D ≥16) including the insurance and AMH variables in the first block, T1 ALE loss and threat subscales and T1 FPI sexual, social, and relationship concerns subscales in the second block, and T1 WOC avoidant coping subscale in the third block was significant (χ^2 [n = 64] = 42.28; df = 8; $P<.001$). The Hosmer-Lemeshow (H-L) goodness-of-fit statistic was not significant ($P=.781$), suggesting a good model fit. The log odds of being diagnosed with depression was related to higher elevations on T1 WOC avoidant coping subscale [odds ratio [OR] 1.90, 95% confidence interval [CI] 1.08–3.34]. Nagelkerke R^2, a measure of strength of association between the predictors and the dependent variable, was 0.781 for the entire model (96.9% correctly classified). This demonstrates that depression at T1 was largely driven by engagement in a problematic coping strategy, namely avoidant coping.

On evaluation of the log-likelihood test of the overall model for T1 anxiety (STAI-S ≥39) including the insurance variable in the first block, the T1 ALE loss and threat subscales and T1 FPI sexual, social, and relationship concerns subscales in the second block, and T1 WOC avoidant coping and information seeking subscales in the third block, the model was significant (χ^2 [n = 76] = 38.34; df = 8; P<.001). The H-L goodness-of-fit statistic was not significant (P=.561), suggesting a good model fit. The log odds of having a score ≥39 was related to poorer insurance coverage (OR 2.49, 95% CI 1.30–4.77), higher elevations on T1 FPI sexual concerns subscale (OR 1.16, 95% CI 1.01–1.32), and higher elevations on T1 WOC avoidant coping subscale (OR 1.13, 95% CI 1.01–1.28). Nagelkerke R^2 was 0.561 for the entire model (80.3% correctly classified). This demonstrates that anxiety at T1 was driven by financial and sexual problems as well as engagement in avoidant coping.

At T2, evaluation of the log-likelihood test of the overall model for depression (CES-D ≥ 16) including the T2 ALE loss and threat subscales, and T2 WOC avoidant coping subscale, and T1 FPI sexual, social, and relationship concerns subscales in the model was significant (χ^2 [n = 58] = 24.457; df = 6; P<.001). The H-L goodness-of-fit statistic was not significant (P=.883), suggesting a good model fit. The log odds of being diagnosed with depression was related to higher elevations on the T2 WOC avoidant coping subscale (OR 1.21, 95% CI 1.00–1.45). Nagelkerke R^2 was 0.525 for the entire model (81.0% correctly classified). As with depression at T1, this demonstrates that depression at T2 was driven by engagement in avoidant coping.

On evaluation of the log-likelihood test of the overall model for T2 anxiety (STAI-S ≥39) including the T2 ALE loss and threat subscales and T1 FPI sexual and social concerns subscales in the first block and T2 WOC avoidant coping subscale in the second block, the model was significant (χ^2 [n = 62] = 20.76; df = 5; P=.001). The H-L goodness-of-fit statistic was not significant (P=.955), suggesting a good model fit. The log odds of having a score ≥39 was related to higher elevations on T2 ALE threat subscale (OR 1.24, 95% CI 1.02–1.52). Nagelkerke R^2 was 0.380 for the entire model (74.2% correctly classified). This demonstrates that at T2, patients with the most anxiety were those who anticipated that treatment would have a negative physical or emotional outcome.

Last, regarding medical treatment data, median scores and significant group differences for the FP patients and the infertile comparison group are listed in Table 4. Thirty-one FP patients had embryos cryopreserved, and 15 had oocytes cryopreserved. One patient was unable to have either oocytes or embryos cryopreserved. Regarding the disposition of unused frozen embryos, 60% of FP and 30% of the infertile comparison group directed the embryos to be donated for research, 15% of FP and 26% of the infertile comparison group would donate them to another couple, and 22% of FP and 11% of the infertile comparison group designated their unused embryos to be discarded (χ^2 = 22.7; P<.000). At the time of writing, one FP woman had returned ~1 year after her embryos were created to use her embryos via a gestational carrier and has an ongoing pregnancy. There was no relationship between clinical pregnancy and CES-D or STAI-S scores at either time point, nor was there a relationship between clinical pregnancy and change in CES-D or STAI-S score from T1 to T2 in the infertile comparison group.

DISCUSSION

Fertility treatment was associated with emotional distress for both cancer patients and the infertile comparison group, and this distress worsened during the treatment cycle for the infertile comparison group. With the use of a CES-D score ≥16 and an STAI-S score ≥39, the majority of FP patients and a substantial minority of the infertile comparison group could be classified as having a clinically significant level of depressive and/or anxiety symptoms at enrollment for fertility treatment. This is in contrast to the lower level of patient self-reported symptoms of depression or anxiety at T1 during the psychologic consultation. The discrepancy between self-reported depressive symptoms during consultation and classification of depression based on the CES-D scores in FP and infertile women was somewhat unexpected. Research finds that many patients underreport mental health symptoms and treatment histories to their medical providers (51, 52). The discrepancy between self-reported history and mood scale scores may therefore be a function of the social desirability to underreport such symptoms during the psychologic consultation.

In the present study, women beginning FP treatment reported higher levels of depression and anxiety symptoms

TABLE 4

Medical data for non–chemotherapy-exposed fertility preservation and infertile control participants who completed a cycle of controlled ovarian hyperstimulation, median (range).

Variable	Fertility preservation	Infertile control
AMH[a]	1.34 (0.2–10.70)	2.05 (0.10–17.26)
Total FSH/LH dose	4,312.5 (2,250.0–10,500.0)	4,125.0 (825.0–9,750.0)
Days stimulated	11.0 (8–15)	11.0 (8–14)
Peak E_2, pg/ml[a]	1,709.0 (351–3,013.0)	2,424.0 (681.0–6,852.0)
Oocytes retrieved	14.0 (0–41)	11.0 (1–37)

Note: Data for infertile control subjects (n = 7) and fertility preservation patients (n = 2) who had their cycle canceled or did not begin a cycle of controlled ovarian hyperstimulation were excluded from all but AMH and Oocytes retrieved data points. AMH = antimüllerian hormone.
[a] P< .05 (group difference; independent-samples Kruskal-Wallis tests followed by Mann Whitney U tests).

Lawson. Depression and anxiety in fertility patients. Fertil Steril 2014.

compared with infertile patients. However, the relatively high levels of depression and anxiety among FP women at T1 did not worsen as the women went through treatment. In contrast, levels of depression and anxiety in the infertile comparison group increased over the course of treatment and matched the high levels seen in the FP group, with at least one-half of women reporting significant symptoms of depression and/or anxiety. It is unclear why the infertile patients' symptoms worsened over time. It is possible that differences in the medical aspects of IVF or longer time intervals between T1 and T2 for the infertile comparison group provided greater opportunity for symptoms of depression and anxiety to develop. However, this does not appear to be the case in our study, because neither the medical aspects of IVF nor time between surveys predicted increased scores on the measures of depression or anxiety. Another hypothesis would be that mood symptoms worsened for the infertile comparison group as they got closer to learning whether or not IVF would result in a pregnancy. The significant increase in anxiety for the infertile comparison group has been previously reported (53, 54) in longitudinal IVF studies, and others have noted that the time of retrieval (55) or following embryo transfer (56) are times of high anxiety for women undergoing IVF. Recent research, however, found no change in anxiety at multiple time points during stimulation, retrieval, and awaiting pregnancy results, although elevations in scores on measures of anxiety were noted at all time points (57). It is also possible that less social desirability existed in the FP patients, because it is generally accepted that a cancer diagnosis will result in distress, whereas the infertile comparison group may have worried that acknowledging symptoms of depression or anxiety would negatively affect their ability to proceed with IVF. Alternatively, FP patients' high initial scores on the depression and anxiety measures may reflect their distress due to the recent diagnosis of cancer and the stress of future cancer treatment (e.g., chemotherapy and radiation). FP patients are also not concerned about immediate pregnancy results, because FP treatment helps them to delay family building until their cancer treatment is complete. Therefore, anxiety and depression levels in FP patients may be elevated and stay elevated because completing FP treatment does not represent the end of their medical ordeal, just the end of a part of it. Additional assessment at a more distant time point could clarify this finding.

According to Lazarus and Folkman's (27) model of stress, appraisal, and coping, individuals who experience an event that they perceive to be stressful and then are unable to adequately cope with that event are at risk for depression and/or anxiety. For example, if a woman experienced a traumatic event that she perceived as upsetting and subsequently engaged in avoidant coping rather than active coping strategies, she would be at increased risk of for depression and/or anxiety. In the context of our study, we hypothesized that patients who developed significant depressive or anxiety symptoms likely appraised fertility treatment as distressing. Although we did not see an increase in the appraisal of threat or loss in the infertile comparison group over time, higher scores on the threat and loss subscales were positively related to higher scores on the CES-D and STAI-S. Consistent with earlier research, three subscales of the FPI (sexual, social, and relationship concerns), a measure of perceived stress (49), also correlated with higher depressive and anxious symptomatology, thus supporting our hypothesis. We also hypothesized that maladaptive coping strategies would be related to depression and anxiety, and indeed avoidance-based coping (WOC SBA) and information and emotional support seeking (WOC IES) were associated with greater psychologic distress. It is not surprising that the WOC IES correlated with anxiety at T1, because this subscale assesses use of the internet for information gathering, and research has found that such coping strategies may result in increased distress (58). The WOC IES subscale includes both positive (emotional support seeking) and potentially negative (use of the internet) coping strategies which likely contributed to its limited contribution to explained variance in the logistic regression model of anxiety. WOC SBA, however, accounted for the greatest unique amount of overall explained model variance in T1 and T2 depression, and it contributed (along with fertility-related sexual concerns and limited insurance coverage for treatment) to the prediction of T1 anxiety. From the perspective of coping, there were no significant differences in coping across time for the infertile comparison group and a significant decrease in information and emotional support seeking coping for the FP group. It may be that compared with FP patients, the infertile comparison group's prolonged engagement in the perceived threatening experience (IVF) and continued inability to actively cope with the experience (avoidant coping) resulted in increased symptomatology over time. Regardless of the explanation for initial psychologic distress or change in distress over time, early patient screening for avoidant coping and/or negative appraisals of IVF could be used to identify and treat patients at risk for increased depression or anxiety at time of oocyte retrieval.

This study is limited by the description of the experiences at a single fertility center with a demographically homogeneous sample. However, this was a preliminary study to highlight areas of future multicenter studies of this patient population. Future research may also be limited by a homogeneous subject group because only patients who have access to medical care and can afford fertility preservation or IVF will likely present for treatment and be available for clinical study. Our sample of FP patients was also limited to those women who self-select for treatment. In our clinic since 2005, we have found that approximately one-third of referred cancer patients opt to undergo FP. This is consistent or somewhat lower than rates found in other clinics (16, 34, 59, 60), although definitions of enrollment greatly differ across studies. It is unclear if patients who pursue FP do so because they are less distressed than non-FP cancer patients or because they are more distressed (about their fertility) than non-FP cancer patients. Regardless, the FP patients in this study reported significant symptoms of depression and anxiety. Finally, this study is also limited by the administration of questionnaires at only two time points before pregnancy results. However, the study is ongoing with additional data collection scheduled for participants.

To our knowledge, this is the first study to prospectively report on the psychologic status of FP patients during FP treatment and to compare FP patients with an infertile comparison group. Although our sample size precluded an ability to conduct logistic regression analyses for each treatment group, such results would not be expected to differ between groups, because the theory of stress, appraisal, and coping is theorized to function similarly across all types of stressors (e.g., medical conditions). It is evident from the present study that anxiety and depression in FP and infertile patients is clinically significant and warrants early intervention from the IVF team and mental health professionals. Early assessment of avoidant coping in patients is warranted also because patients who engage in such problematic coping are at increased risk of depression and/or anxiety. It is encouraging that medical aspects of IVF (e.g., gonadotropin dose, ovarian reserve markers) do not appear to be associated with increased depression or anxiety. However, IVF programs should routinely assess levels of depression and anxiety among FP and infertile patients and have appropriate support services for these women, because some face the dual challenges of cancer and FP and/or worry about their ability to complete their reproductive dreams.

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